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NOVEL TREATMENT APPROACHES FOR CHILDREN AND ADOLESCENTS WITH OBSESSIVE-COMPULSIVE DISORDER

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Novel treatment approaches for children and adolescents with obsessive-compulsive disorder

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To my family.

ABSTRACT

Background: Obsessive-compulsive disorder (OCD) is a prevalent and disabling condition with typical onset during childhood. The recommended treatment is cognitive behavioral therapy (CBT), but it is seldom available to young people. Previous research has indicated that internet-delivered CBT (ICBT) is an efficacious treatment for adolescents with OCD, but little is known about its feasibility for children and if the treatment is transferrable to other contexts. Further, ICBT has been proposed as a possible first intervention in a stepped care model, but knowledge is lacking about the efficacy and cost-effectiveness of such a model.

Aims: The overall aim of this thesis was to develop and evaluate novel approaches to deliver and scale up the treatment for children and adolescents with OCD. More specifically, the aims were to evaluate (1) the feasibility of ICBT for children 7-11 years with OCD, (2) if the ICBT program is transferrable to clinical units in different countries, and (3) if ICBT in a stepped care model has comparable effects as, and using less resources than, face-to-face CBT for children and adolescents with OCD.

Methods: Study I was an open pilot study where 11 children and their parents received 12 weeks of therapist-guided ICBT (aim 1). In Study II, ICBT was provided to 31 families at three different clinical units located in Gothenburg, London, and Brisbane, to investigate if the treatment is transferrable to other contexts outside the clinic in Stockholm where it was originally developed (aim 2). Study III was a two-site randomized non-inferiority trial where 152 children and adolescents with OCD either received ICBT in a stepped care approach (ICBT for 16 weeks and non-responders were offered face-to-face CBT between the 3-month and 6-month follow-up), or standard face-to-face CBT (16 weeks of face-to-face CBT and non-responders were offered additional face-to-face CBT between the 3-month and 6-month follow-up). The non-inferiority was evaluated at the 6-month follow-up using the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) as the main outcome and the trial incorporated a full economic evaluation (aim 3).

Results: In Study I, the treatment completion was high and both children and their parents were overall very satisfied with the treatment. The results showed a large reduction of OCD symptom severity and improvements on secondary outcomes (e.g., general functioning and family accommodation) after treatment, which were maintained during the follow-up period of three months. In Study II, the number of treatment completers and therapist time differed somewhat between the sites. Overall, results indicated large reductions of OCD symptoms, with additional improvements up to the 3-month follow-up. Further, the therapists reported both advantages and challenges with the online format. In Study III, we could demonstrate that the stepped care treatment was as efficacious as the face-to-face treatment with an estimated mean difference of 0.91 points on the CY-BOCS (95% CI, -1.46 to 3.28, p = .45; 68% responders in both groups), but to a lower cost for the health care provider (average cost saving of -$2104 [95% CI, -3006 to -1202] per participant in the stepped care treatment compared with the face-to-face treatment).

Results remained largely the same also when broadening the economic evaluation to the health care organization perspective and the societal perspective.

Conclusions: Therapist-guided ICBT is a feasible intervention for both children and adolescents with OCD, also when delivered in other settings and countries than the clinic in Stockholm (Sweden). ICBT can be provided as a first treatment step where patients who do not respond sufficiently subsequently receive face-to-face CBT. This stepped care approach provides equal treatment effect as standard face-to-face CBT while at the same time being cost-saving for the health care provider. Though most importantly, ICBT could greatly increase access to evidence-based treatment so more children and adolescents with OCD can get the help they need and deserve.

SAMMANFATTNING

Bakgrund: Tvångssyndrom är en vanligt förekommande och funktionsnedsättande sjukdom som oftast debuterar under barndomen. Den rekommenderade behandlingen är kognitiv beteendeterapi (KBT), men tillgängligheten till behandling är ofta låg för barn och ungdomar. Tidigare forskning har visat att internetförmedlad KBT (IKBT) är en effektiv behandling för ungdomar med tvångssyndrom, men vi vet lite om dess genomförbarhet för barn samt om behandlingen är överförbar till andra sammanhang. IKBT har föreslagits vara en möjlig första behandlingsinsats i en stegvis vårdmodell, men kunskap saknas om effekten och kostnads-effektiviteten av en sådan modell.

Syfte: Det övergripande syftet med avhandlingen var att utveckla och utvärdera nya tillvägagångssätt för att förmedla och öka tillgängligheten till behandling för barn och ungdomar med tvångssyndrom. Mer specifikt var syftena att utvärdera (1) genomförbarheten av IKBT för barn 7–11 år med tvångssyndrom, (2) om IKBT behandlingen är överförbar till kliniska mottagningar i olika länder och (3) om IKBT i en stegvis vårdmodell har jämförbara effekter som, men använder mindre resurser än, traditionell KBT för barn och ungdomar med tvångssyndrom.

Metod: Studie I var en öppen pilotstudie där 11 barn och deras föräldrar fick 12 veckors terapeutledd IKBT (syfte 1). I Studie II gavs IKBT till 31 familjer på tre kliniska mottagningar i Göteborg, London och Brisbane. Studien undersökte om behandlingen är överförbar till andra sammanhang utanför mottagningen i Stockholm där den ursprungligen utvecklades (syfte 2). Studie III var en randomiserad non-inferiority studie som genomfördes på två mottagningar, där 152 barn och ungdomar med tvångssyndrom antingen fick IKBT i en stegvis vårdmodell (IKBT under 16 veckor och de som inte fått tillräcklig effekt erbjöds traditionell KBT mellan 3-månaders och 6-månadersuppföljningarna) eller traditionell KBT (KBT under 16 veckor och de som inte fått tillräcklig effekt erbjöds mer av samma behandling mellan 3-månaders och 6-månadersuppföljningarna). Effekten utvärderades vid 6-månadersuppföljningen med Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) som huvudutfallsmått och studien inkluderade en fullständig ekonomisk utvärdering (syfte 3).

Resultat: I Studie I genomförde deltagarna större delen av behandlingen och både barn och föräldrar var generellt väldigt nöjda med behandlingen. Resultaten visade en stor symtomreduktion och förbättringar på sekundära utfallsmått (t.ex. generellt fungerande och familjeanpassningar) efter behandlingen, vilket kvarstod under uppföljningsperioden på tre månader. I Studie II skiljde sig antalet deltagare som genomfört behandlingen och behandlingstiden något mellan mottagningarna. Övergripande så indikerade resultaten en stor minskning av OCD-symtom, med ytterligare förbättringar upp till 3-månadersuppföljningen. Vidare så rapporterade behandlarna både fördelar och utmaningar med behandlingsformatet. I Studie III kunde vi visa att den stegvisa vårdmodellen var lika effektiv som traditionell behandling med en uppskattad mellangruppsskillnad på 0.91 poäng på CY-BOCS (95% KI, -1.46 to 3.28, *p*

= .45; 68% svarade på behandlingen i båda grupperna), men till en lägre kostnad för vårdgivaren (genomsnittlig kostnadsbesparing var -$2104 [95% KI, -3006 to -1202] per deltagare som fick den stegvisa behandlingen jämfört med traditionell behandling). Resultaten kvarstod när den ekonomiska utvärderingen breddades till ett sjukvårdsperspektiv och till ett samhällsperspektiv.

Slutsatser: Terapeutledd IKBT är en genomförbar behandling för både barn och ungdomar med tvångssyndrom, även när den ges i andra sammanhang och länder än på mottagningen i Stockholm. IKBT kan ges som ett första behandlingssteg där patienter som inte får tillräcklig effekt får traditionell KBT efteråt. Den här stegvisa vårdmodellen har likvärdiga behandlingseffekter som traditionell behandling samtidigt som den är kostnadsbesparande för vårdgivaren. Sammantaget kan IKBT kraftigt öka tillgängligheten till evidensbaserad behandling så att fler barn och ungdomar med tvångssyndrom kan få den hjälp de behöver och förtjänar.

LIST OF SCIENTIFIC PAPERS

I. **Aspvall, K.**, Andrén, P., Lenhard, F., Andersson, E., Mataix-Cols, D., & Serlachius, E. (2018). Internet-delivered cognitive behavioural therapy for young children with obsessive–compulsive disorder: development and initial evaluation of the BIP OCD Junior programme. *BJPsych Open, 4*(3), 106-112.

II. **Aspvall, K.,** Lenhard, F., Melin, K., Krebs, G., Norlin, L., Näsström, K., Jassi, A., Turner, C., Knoetze, E., Serlachius, E., Andersson, E., & Mataix-Cols, D. (2020). Implementation of internet-delivered cognitive behaviour therapy for pediatric obsessive-compulsive disorder: Lessons from clinics in Sweden, United Kingdom and Australia. *Internet Interventions, 20*, 100308.

III. **Aspvall, K.,** Andersson, E., Melin, K., Norlin, L., Eriksson, V., Vigerland, S., Jolstedt, M., Silverberg-Mörse, M., Wallin, L., Sampaio, F., Feldman, I., Bottai, M., Lenhard, F., Mataix-Cols, D., & Serlachius, E. Stepped-care internet-delivered versus face-to-face cognitive-behavior therapy for pediatric obsessive-compulsive disorder: a randomized clinical non-inferiority trial. *Unpublished manuscript.*

Appendix:
Aspvall, K., Andersson, E., Lenhard, F., Melin, K., Norlin, L., Wallin, L., Silverberg-Mörse, M., Feldman, I., Bottai, M., Mataix-Cols, D., & Serlachius, E. (2019). Stepped Care Internet-Delivered vs Face-to-Face Cognitive-Behavior Therapy for Pediatric Obsessive-Compulsive Disorder: A Trial Protocol for a Randomized Noninferiority Trial. *JAMA network open, 2*(10), e1913810.

CONTENTS

LIST OF ABBREVIATIONS

ASD	Autism spectrum disorder
BIP	Barninternetprojektet (*child internet project)*
CAMHS	Child and adolescent mental health services
CBT	Cognitive behavioral therapy
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
ERP	Exposure with response prevention
ICBT	Internet-delivered cognitive behavioral therapy
NordLOTS	Nordic Long-Term OCD Treatment Study
OCD	Obsessive-compulsive disorder
PANDAS	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PANS	Pediatric acute-onset neuropsychiatric syndrome
RCT	Randomized controlled trial
SRIs	Serotonin reuptake inhibitors

1 INTRODUCTION

When looking back on how the journey with this thesis started, I have to go all the way back to my last year as a psychology student at Karolinska Institutet. The first patient I had during my clinical training had obsessive-compulsive disorder (OCD). I was fascinated to see how effective psychological treatment can be for this patient group, especially since the disorder has such a large impact on the patients' well-being and can control many aspects of the daily life. This sparked my interest and got me to start working clinically with OCD, both during my internship as well as when working as a clinical psychologist. I have continued to be amazed by the tremendous impact a psychological intervention can have for the patients as well as their families. However, it also became very clear to me that there is a major supply and demand gap in Sweden and many young people with OCD do not receive the proper help in time, even though providing treatment early in life is a very important goal for this patient group.

In 2015, I became a PhD student and my aim was to develop and evaluate novel treatment approaches for children and adolescents with OCD. I wanted to develop internet-delivered cognitive behavioral therapy (ICBT) for younger children so they would get a possibility to an intervention early during the disorder trajectory. Further, I was curious to investigate how the ICBT treatment works in different contexts. But above all, I wanted to evaluate if a suitable treatment delivery model could be to deliver ICBT as a first treatment step, and subsequently provide face-to-face treatment as the second step for those who do not benefit sufficiently from the ICBT treatment. The overall goal with the project has been that our ICBT treatment would be disseminated and implemented so more OCD sufferers could get access to an early intervention for the disorder.

For me this has been an amazing journey. The most important experience has been to help out the participating children and adolescents to a better life. I have also had the privilege to work with the amazing clinicians at the child psychiatry units in Stockholm and Gothenburg. I hope this thesis can contribute both scientifically and clinically, by increasing the knowledge about how to make effective treatment more available for children and adolescents with OCD. I want to give them a possibility to take back the control of their lives so they are able to go hiking with their parents, swimming with their sisters and brothers, learn important things in school, and have fun with their friends again.

Stockholm, October 2020

2 BACKGROUND

2.1 OBSESSIVE-COMPULSIVE DISORDER

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by distressing and time-consuming obsessions and compulsions. Obsessions are defined as unwanted intrusive thoughts, images or impulses. Compulsions are defined as behaviors with primary function to reduce or neutralize the distress from the obsession. Compulsions can be either overt behaviors which are visible to others, such as hand-washing and control of electrical appliances, or covert behaviors that are not visible to others, such as mental rituals. Most individuals with OCD experience both obsessions and compulsions, however some children do not have well-defined obsessions or might have difficulties in expressing the aim of the compulsions. To fulfill diagnostic criteria for OCD, the obsessions or compulsions must be time consuming or cause significant distress or impairment for the individual. In addition to the core features of the disorder, DSM-5 has two specifiers to the OCD diagnosis that is related to level of insight and if the disorder is related to tics.[1]

The disorder is heterogeneous with a range of different symptoms. Some research studies have suggested that OCD consist of four different symptom dimensions; 1) obsessions and checking, 2) symmetry and ordering, 3) contamination and cleaning, and 4) hoarding.[2-4] Other studies have suggested five factors of OCD as a result of the identification of an additional OCD dimension also known as taboo thoughts (including aggressive, sexual, and religious obsession).[5,6] Moreover, some research studies have suggested that feeling of incompleteness and harm avoidance could be two core motivational processes in OCD, irrespective of which form of ritual the patient engage in.[7] One recent study has indicated that harm avoidance could be related to doubting/checking, obsessing and washing, and feeling of incompleteness to doubting/checking, ordering and neutralizing.[8]

2.2 IMPACT OF THE DISORDER

OCD affects about 0.25-3% of children and adolescents,[9,10] and has a lifetime prevalence of 2.3%.[11] There seem to be two peaks of onset, with about 76% having an early onset during childhood, and the other average onset is later around 23 years.[12] Early onset is associated with increased level of tics and greater symptom severity. Previous research has shown that some individuals improve over time, but about 40% of children and 50% of adults continue to have long-term clinically OCD symptoms.[13-15]

Children with OCD experience impairments in many important areas of functioning, such as at home (problems with the family) and social situations (problem with friends),[16] and one study have indicated that young people with OCD are about 50% less likely to access and finish secondary school.[17] In a longer perspective, nearly 44% of adults with OCD have difficulties to participate in the labor market (compared with about 16% of individuals in the general population),[18] and the disorder has also been associated with an almost ten-fold risk of dying by suicide,[19] as well as elevated prevalence of cardiovascular diseases.[20]

The majority of OCD sufferers have at least one comorbid disorder, where the most common are major depressive disorder, anxiety disorders, tic disorders, attention-deficit/hyperactivity disorder, autism spectrum disorder (ASD), and oppositional defiant disorder.[21,22]

2.3 ETIOLOGY AND MAINTENANCE

2.3.1 Etiology

Many factors contribute to the development of OCD, but the exact causes of the disorder are still unclear. Since many factors seem to contribute, an integrative model of the etiology of OCD has been proposed, where genetic, environmental and neuropsychological processes interact.[23] Studies have shown that OCD is a heritable disorder with about 40% of the variance attributed to genetic factors,[23,24] and the genetic influence might be higher among childhood-onset OCD.[23] Three studies have to date made gene searching efforts and they have been largely unsuccessful,[25-27] where only one single nucleotide polymorphism that is associated with OCD symptoms has been found to exceed the accepted level of statistical significance.[27] Further, studies have found that genes related to serotonin, dopamine and glutamate-systems are involved in the expression of OCD.[23]

Most of the research on the role of environmental factors (e.g., perinatal complications, reproductive cycle, and stressful and traumatic life events) in the development of OCD have used retrospectively collected data which limits the possibility to make any firm conclusions. However, adverse perinatal events such as maternal smoking, breech presentation, and preterm birth have in a Swedish register-based study been found to increase the risk for OCD.[28]

Further, several studies have tried to explain how infections or inflammations can cause OCD symptoms, such as described in pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS).[29,30] The etiology behind this association is still unknown, and it has been difficult to identify triggers among the patients. Thus, more research is needed to identify prognostic factors or potential biomarkers that could be clinically useful.[31,32]

2.3.2 Psychological models

One of the first psychological theories of OCD was proposed by Mowrer.[33] According to this theory, obsessions are conditioned stimuli associated with a conditional response (e.g., anxiety or distress) which forms a discriminant stimulus for compulsions. In other words, an intrusive thought (e.g., fear of having been contaminated by germs) is associated with anxiety, which elicits behaviors to reduce or neutralize the fear (e.g., washing hands). Performing compulsions leads to negative reinforcement due to temporarily relief of the conditional response, which maintains the relationship between the obsession and conditional response and increase the probability of future compulsions.

Salkovskis and Rachman subsequently added a cognitive element to Mowrer's theory.[34-36] The cognitive framework emphasizes the importance of obsessive beliefs, i.e., how the individual

interprets the meaning of the thoughts (similar to metacognitions). If the individual perceives the obsessions as a signal that something is wrong and has a belief that it is ones' responsibility to prevent bad things from happening, then the individual is more prone to perform compulsions compared to an individual that believe that it is normal to have unpleasant thoughts.

The cognitive components are not emphasized as much when it comes to children and adolescents.[37] The common model used to conceptualize OCD and explain the maintenance for children and adolescents builds upon the Mowerian principles.[33] Obsessions are considered to be unwanted thoughts that trigger a rapid response in the form of increased distress, and compulsions are behaviors that are designed to reduce this distress.[37] The compulsions are negatively reinforced, which means that individuals are more prone to act the same way in the future since the compulsions help them reduce something unwanted (i.e., anxiety, distress, or a feared consequence). This leads to OCD being maintained since the associations are strengthened as long as the individual continues to perform the compulsions.

In summary, OCD is defined by impairing obsessions and compulsions that lead to distress and decreased functioning for the individual. Etiological models suggest that genetic factors interact with environmental factors in the development of OCD and models of maintenance (once the disorder is manifested) underscore negative reinforcement as a key factor. More research is needed to fully understand the development and maintenance of the disorder among the youth population.

2.4 TREATMENT

Both national and international guidelines recommend that children and adolescents with OCD should be offered cognitive behavioral therapy (CBT) as psychological treatment and an additional pharmacological treatment if needed.[38-40]

2.4.1 Pharmacological treatment

The first-line pharmacological treatment for pediatric OCD is serotonin reuptake inhibitors (SRIs). SRIs have shown moderate effect sizes compared with pill placebo (g = 0.51, 49% responders),[41] and it is often recommended that this treatment should be combined with CBT for children and adolescents with moderate to severe OCD.[38-40] However, it is important to stress that the recommendation of combined treatment is based on one single trial,[42] and there is no consistent evidence that the combination of SRIs and CBT is more effective than CBT alone for pediatric OCD.[41] Antipsychotic medication is not recommended as routine treatment for pediatric OCD, but can be carefully considered as augmentation when other interventions have not been helpful.[38-40]

2.4.2 Psychological treatment

The gold standard psychological treatment for pediatric OCD is CBT, which is based on the psychological model of maintenance of OCD symptoms presented above. This treatment usually consists of up to 14 weekly 1-hour sessions.[22,42,43] The main treatment component is

exposure with response prevention (ERP), where the patient gradually expose him/herself to the obsessions, while at the same time resist to engage in compulsions.[43] By repeating ERP, the anxiety or distress that is associated with the obsessions is hypothesized to gradually decrease.[44,45] Some research has shown that not everyone experiences this reduction of anxiety (habituation), and another proposed explanation could also be better tolerance for anxiety and increased self-efficacy.[44,46] Beside ERP, treatment protocols typically include psychoeducation, various cognitive strategies and relapse prevention.[37,43]

Most CBT protocols for pediatric OCD include some form of involvement by family members. Including the family in the treatment of pediatric OCD is traditionally regarded as important, but the amount of involvement differ between CBT procotols.[22,42,43,47] One major benefit of involving the family is that the parents can work as co-therapists during the treatment, and reinforce exposure exercises to increase the child's motivation.[43] Additionally, many behaviors performed by family members can actually maintain the OCD (i.e., family accommodation behaviors), and this is more easily addressed if the family is involved in the treatment.[48]

CBT has consistently shown large effect sizes compared to both waitlist and placebo (g = 0.93-1.53, 70% responders) in 25 randomized controlled trials (RCTs),[41] and has also sustained long-term gains.[49,50] Interestingly, CBT has been shown to be an effective augmentation treatment for non-responders to both SRIs and first attempt with CBT,[51-53] which indicates that providing more CBT could be beneficial for individuals with previous insufficient response to treatment.

Despite expert consensus and guidelines recommending CBT, accessibility is low and a majority of OCD sufferers do not receive this evidence-based treatment.[52,54] Possible barriers include the low number of properly trained CBT therapists within the health care system and also financial and geographical barriers.[55,56] Different approaches have been done to solve this problem, including development of digital treatment alternatives.

2.4.3 New technologies to deliver CBT

As one way to increase the availability to treatment, new technology-based approaches to deliver CBT remotely have been developed, such as video-conferencing,[57,58] telephone-CBT,[59] and internet-delivered CBT (ICBT).[60-62] All approaches have about the same content as regular face-to-face CBT and provide an opportunity to improve the reach of treatment as the sessions are non-office-based. Both video-conferencing and telephone-CBT include scheduled real-time sessions with a therapist, whereas ICBT is delivered as a self-help book at an online platform and can be either self-guided or delivered with asynchronous therapist-support.[63] The therapist-guided ICBT programs requires less therapist time to other treatment options such as face-to-face CBT,[22,42,43] video-conferencing,[57,58] and telephone-CBT,[59] which has apparent advantages from a resource use perspective since therapists can treat more patients at the same time.

The development of ICBT for children and adolescents with OCD is lagging behind the adult field, where therapist-guided ICBT for OCD has already been implemented in the regular

health care system in both Australia and Sweden.[64] Several studies have demonstrated that ICBT is effective for adults with OCD,[65-67] and the treatment is currently being evaluated compared to face-to-face CBT in a non-inferiority trial.[68] For the younger population, there are currently two ICBT interventions available for adolescents with OCD. One is a self-guided intervention developed in Australia called "OCD? Not me!".[69] Preliminary results from an open trial (N = 132) indicated moderate symptom reductions on self-rated OCD severity (within-group Cohen's d = 0.89).[62]

The other ICBT intervention that has recently been developed is the Swedish program "BIP OCD". The BIP OCD treatment is provided completely online with support by a designated therapist who has asynchronous contact with both the adolescent and the caregiver through an encrypted website. The treatment consists of 12 modules for the adolescent and five parallel modules for the parents. BIP OCD has been evaluated in one open pilot study (N = 21) with promising results (Cohen's d = 2.29, 57% responders).[60] The results from a subsequent waitlist-controlled RCT (N = 67) showed weaker effects at posttreatment compared with the pilot study (between-group Cohen's d = 0.69),[61] though the effects improved during the naturalistic follow-up after three months (within-group Cohen's d = 1.68, 32% responders and 26% remitters),[61] as well as one year posttreatment (within-group Cohen's d = 2.15, 73% responders and 40% remitters).[70]

However, the treatment effects do not seem to be as high as in face-to face CBT. ICBT could thus function as a first-line intervention in a stepped care model for OCD, where the treatment intensity can be increased by providing face-to-face treatment for the ones that do not respond sufficiently to the first course of treatment.[39,61,71] For OCD, such an approach has so far only been evaluated for adults with bibliotherapy as the first treatment step.[72-74] Thus, ICBT in a stepped care model has never been empirically tested yet. Additionally, it is unclear if BIP OCD is feasible for younger children with OCD, and if the treatment is transferrable to other context as it has so far not been tested outside the clinical-academic setting in Stockholm (Sweden).

2.4.4 Cost-effectiveness

Cost-effectiveness analyses are crucial when new treatments are to be fitted in an existing health care model, as both the efficiency and the cost of the new intervention is analyzed in relation to an already existing treatment. The difference in costs in relation to the difference in outcome between two intervention groups can for instance guide decisions on how to allocate resources within the health care system.[75] The costs can also be estimated from different perspectives, e.g., the health care provider (intervention costs), the health care organization (health care visits and medication use) or the society as a whole (other direct costs such as social support as well as indirect costs such as being absent from work and school or less productive when attending work or school).[75]

Overall, ICBT is suggested to be a cost-effective treatment option, since it typically involves less therapist resources compared to face-to-face interventions and leads to better health

outcomes than not receiving any treatment.[76,77] There are however limited economic evaluations of ICBT for OCD, and only two studies for adults and one for adolescents have been published to date.[78-80] The first study for adults with OCD showed ICBT to be a cost-effective treatment option from both the health care provider and the societal perspective compared to online supportive therapy.[79] The second study for adults found that ICBT was a cost-effective treatment option compared with face-to-face CBT.[80] However, this study used simulated data on face-to-face CBT, i.e., there were no direct comparison between the two treatment options. The study investigating the cost-effectiveness of ICBT for adolescents with OCD was conducted as a part of the BIP OCD RCT mentioned above.[78] The average therapist support time was only 17.5 minutes per patient and week,[61] and ICBT led to a societal cost saving in regard of reduced health care use, supportive resources, school absenteeism, and productivity loss compared with the group that did not receive any treatment.[78] Further, there are to date only one economic evaluation of stepped care treatment for OCD, showing that bibliotherapy followed by face-to-face CBT is cost-saving compared to standard CBT for adult OCD.[74]

In summary, ICBT could be a cost-effective treatment option, but current research gaps call for further evaluations before recommendations for policy makers can be made. Since ICBT is suggested to be implemented within a stepped care model, an economic evaluation should be conducted of such an approach, where the effect is established against existing treatment options.

2.5 SUMMARY

OCD is a heterogeneous, prevalent and impairing disorder with typical onset during childhood. CBT is the gold standard treatment option for pediatric OCD, and providing more CBT for non-responders to first-attempt of CBT seems to be beneficial. However, the availability to CBT is low and different approaches have been developed to solve this problem. One such solution is therapist-guided ICBT that has showed promising results for adolescents with OCD. However, one important research gap is whether this form of treatment also is suitable for younger children with OCD. Another research gap is if the treatment is feasible in other countries and contexts than it was originally developed. Further, although therapist-guided ICBT is one promising option, the effects may not be as robust as expected in face-to-face CBT. Thus, implementing this treatment on a large scale would still not solve the issue with availability to treatment for all patients with OCD. Instead one idea could be to provide ICBT in a stepwise fashion, with face-to-face CBT as a second subsequent step for patients who fail to respond sufficiently to ICBT. This treatment approach has the potential to be both scalable and cost-effective with long-term sustained efficacy.

3 RESEARCH AIMS

The overall aim of this thesis was to develop and evaluate novel approaches to deliver and scale up the treatment for children and adolescents with OCD. The specific aims of each study are presented below.

3.1 STUDY I: FEASIBILITY PILOT STUDY FOR CHILDREN WITH OCD

The aim of this study was to evaluate if ICBT is a feasible and potentially effective intervention for young children aged 7-11 years with OCD. The main hypothesis was that the treatment would be acceptable and feasible for the patient group, and lead to a significant reduction in OCD symptoms and improvement in general functioning.

3.2 STUDY II: IMPLEMENTATION STUDY IN DIFFERENT COUNTRIES

This study evaluated if ICBT is feasible and potentially effective when implemented in clinical units in different countries. More specifically, the BIP OCD treatment was evaluated at two specialist units for OCD in Gothenburg and London and at a university clinic in Brisbane. The hypothesis was that the treatment would be effective when delivered outside the research setting in Stockholm where the treatment was originally developed. Another aim was to explore the experiences of the therapists who participated in the study.

3.3 STUDY III: RANDOMIZED NON-INFERIORITY TRIAL WITH ECONOMIC ANALYSIS

The aim of Study III was to evaluate if ICBT in a stepped care model is non-inferior and cost-effective compared with gold standard face-to-face CBT for children and adolescents with OCD. The hypotheses were that stepped care ICBT would be non-inferior to face-to-face CBT in reducing OCD symptoms, while at the same time being a cost-effective treatment associated with lower intervention costs compared to face-to-face CBT. A secondary aim was to explore if source of referral (clinician-referred versus self-referred) is a moderator of treatment outcome.

4 THE EMPIRICAL STUDIES

4.1 THE TREATMENT

The BIP OCD program has previously been evaluated for adolescents,[60,61] and a child adapted version was developed as a part of Study I. The two age-adapted versions of the program have been developed using an iterative approach and an update has been made between each conducted trial based on feedback from therapists and participating families. The updates have included for example more video material, information about avoidance behaviors and specific examples on ERP for just-right symptoms. All versions are based on standard CBT protocols for treating children and adolescents with OCD,[43,59] and consist of 12 or 14 modules depending on the version. The modules are delivered consecutively and the families are encouraged to work with one module every week. The initial modules for the participants include education about OCD, the OCD circle, and the rational for ERP. Then the main focus is on performing ERP exercises, and some new information is provided in each module, e.g., including how to reduce family accommodation, exposure for obsessions, reexposure techniques, and how to reduce avoidance behaviors. The final chapter includes a treatment summary and relapse prevention, and this module is always offered during the last week of treatment regardless of how many previous modules the families have completed. All information is presented in an engaging age-adapted way, with texts, movies, examples, and interactive worksheets (see Figure 1 for screenshots).

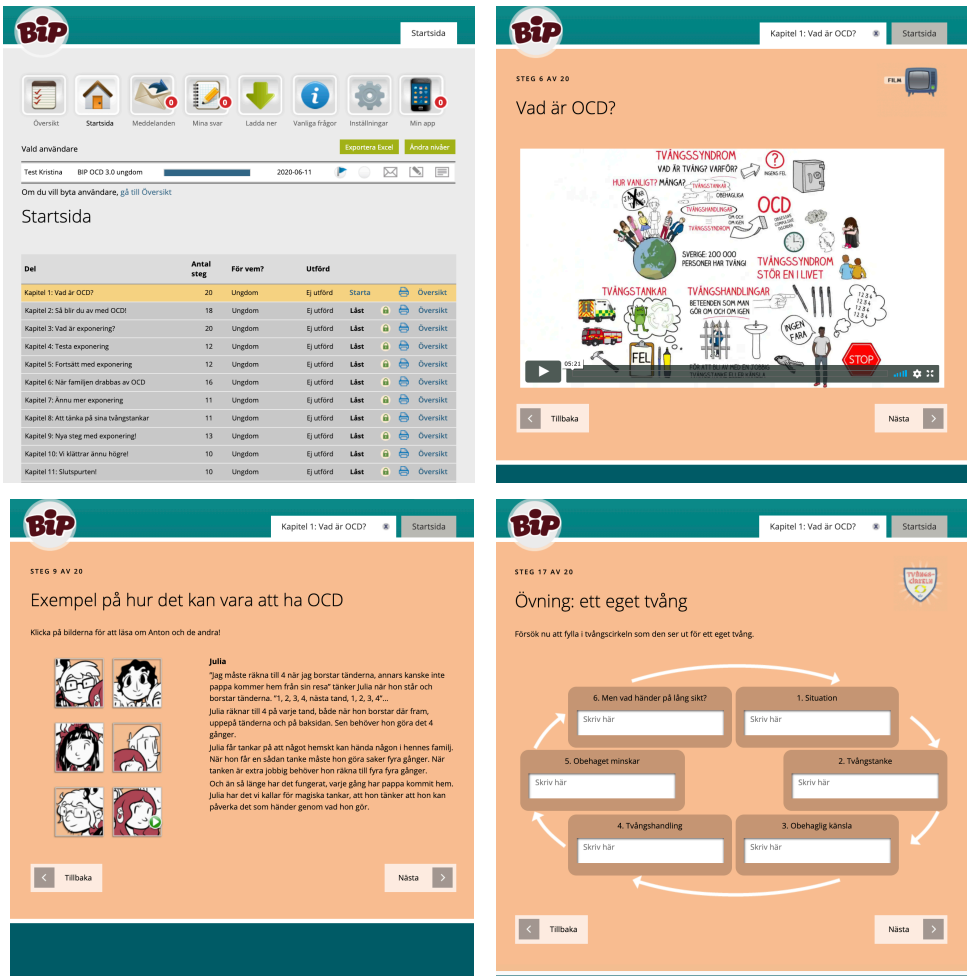

Figure 1. Screenshots of BIP OCD: the treatment overview, a video with education about OCD, examples patients in the treatment and an exercise with the OCD circle.

The parents have a separate login to the treatment platform and receive equal number of modules as their child. The aim of the parental modules is to provide more in-depth information about OCD and the treatment, present strategies for helping the children cope with their OCD and how to best provide support during exposure exercises. It also includes information and exercises on how to use positive reinforcement depending on the child or adolescent's way of functioning, and on how to reduce parental accommodation (i.e., parental adaptations in the everyday life due to the child's OCD, such as responding to reassure questions or participating in compulsive behaviors).

Throughout the treatment period, the families have the possibility to have daily contact with a dedicated therapist, who support the families, gives further explanations if needed, encourage them to continue with the presented strategies, and remind them when being inactive. Feedback from the therapist is given through a built-in messaging function similar to e-mail, and by commenting on worksheets that the participant and parents have completed. The therapist also has a possibility to call the families if needed. See https://vimeo.com/355965105/b3d5d1c439 for an overview of BIP OCD.

4.2 STUDY I

4.2.1 Methods

Study I was a feasibility study using an open trial design that included 11 children 7-11 years old with OCD and at least one of their parents or legal guardians. The study was conducted at the Child and Adolescent Psychiatry Research Unit within the Child and Adolescent Mental Health Services (CAMHS) in Stockholm (Sweden). The participants received the therapist-guided ICBT treatment "BIP OCD junior" during 12 weeks. The treatment consists of 12 modules for the child and parent each. Assessments were conducted by a psychologist before and after the treatment as well as three months after treatment completion. The primary outcome measure was the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) and secondary outcome measures included child- and parent-rated measures of OCD symptoms, depressive symptoms, general functioning and family accommodation. Treatment credibility, adherence, and patient satisfaction were used as feasibility measures.

4.2.2 Main results

Participants and their parents reported that the ICBT treatment was credible and that they were satisfied with the treatment. The treatment completion was high (both children and parents completed on average 11 of the 12 modules) and data attrition low, which indicates that BIP OCD junior is a feasible intervention for this young patient group. A large within-group effect on OCD symptom severity was found at posttreatment (Cohen's $d = 1.86$, 95% CI 0.83 to 2.86), which was maintained during the follow-up period. Similar results were found for the secondary outcome measures. At the 3-month follow-up, 73% were responders and 64% were in remission.

4.3 STUDY II

4.3.1 Method

In Study II, BIP OCD was evaluated for children and adolescents with OCD on three different sites using open trial design. The sites were two specialist CAMHS units for OCD located in Gothenburg (Sweden) and London (United Kingdom) and a university clinic in Brisbane (Australia). All 31 participants and at least one of their caregivers received one of the two language versions (Swedish or English) of BIP OCD during 12 weeks. Number of completed modules and treatment completers were used as adherence measures. Participants were assessed with the primary outcome measure CY-BOCS at pretreatment, posttreatment and at 3-month follow-up. All therapists involved in the trial provided feedback on the feasibility and acceptability of the treatment.

4.3.2 Main results

A majority (80%) of the participants were clinician-referred. There were no significant difference on module completion that was on average high (M = 8.1/12; F(2)=1.22, p = .31), however number of treatment completers (100% in Gothenburg and 56% in London and Brisbane; χ^2 (2, N = 31) = 8.79, p = .02) and average therapist time per patient and week (45 minutes in Gothenburg and 19 minutes in London and Brisbane; (F(2) = 25.64, p < .000) differed by site. A large reduction of OCD symptom severity was observed at posttreatment (bootstrapped Cohen's d = 1.78, 95% CI 1.18 to 2.39), with a further additional reduction up to the 3-month follow-up (bootstrapped Cohen's d = 0.27, 95% CI 0.02 to 0.51). Similar results were found on the secondary outcome measures. The therapists reported both advantages (e.g., efficient for therapists, convenient for families, and the high amount of parental involvement) and challenges (e.g., engage patients throughout the treatment, not suitable for all patients) with the treatment format. Overall, the results support that BIP OCD is a feasible treatment when delivered in regular clinics.

4.4 STUDY III

4.4.1 Methods

Study III was a randomized non-inferiority trial evaluating the efficacy and cost-effectiveness of ICBT in a stepped care model compared with face-to-face CBT for children and adolescents (N = 152) with a primary diagnosis of OCD. The study setting was two specialist CAMHS units for OCD in Stockholm and Gothenburg (Sweden). The participants who were randomized to the stepped care group received 14 modules of ICBT during 16 weeks, and the participants who were classified as non-responders (defined as < 35% reduction on CY-BOCS and/or a Clinical Global Impression-Improvement score > 2)[81] at the 3-month follow-up were offered face-to-face CBT with up to 12 sessions before the 6-month follow-up. Participants who were randomized to the gold standard group received face-to-face CBT with up to 14 sessions during 16 weeks, and non-responders were offered more of the same treatment at the 3-month follow-up. Masked assessments were conducted at pretreatment, posttreatment, 3-month follow-up

and 6-month follow-up (primary endpoint). The non-inferiority was evaluated at the 6-month follow-up using mixed-effect regression analyses for repeated measures and the non-inferiority margin was set to 4 points on the primary outcome measure (CY-BOCS). Cost-effectiveness analyses were conducted from both a health care provider perspective (including treatment costs only), a health care organization perspective (including other self-reported health-care related costs), and a societal perspective (including resources related to social support and indirect costs such as school and work absenteeism).

4.4.2 Main results

Data on the primary outcome measure was available for 99% of the participants at the primary endpoint (Figure 2). The mean CY-BOCS score at the primary endpoint was 11.57 points (*SD* = 6.40) in the stepped care group and 10.57 points (*SD* = 7.57) in the face-to-face treatment group (Figure 3). The intention-to-treat analysis showed that the estimated mean difference on the CY-BOCS was 0.91 points (95% CI -1.46 to 3.28, $p = .45$). This indicates that the stepped care treatment was non-inferior to face-to-face treatment, since the upper boundary of the two-sided confidence interval of the mean difference was below the predefined margin of 4 points. There was no support of a between-group interaction with source of referral ($B = 0.07$; $Z = 0.86$; $p = .39$). The proportion of participants being responders at the 6-month follow-up were 68% in both groups. The total cost per patient for the stepped care treatment was $3343 (*SE* = 22) and $5395 (*SE* = 364) for participants in the face-to-face treatment. This corresponds to an average cost saving of -$2104 (95% CI -3006 to -1202) per patient in the stepped care group compared to the face-to-face treatment. The results were maintained when broadening both to a health care organization perspective and a societal perspective. Participants reported similar occurrence of undesirable effects throughout the study period in the two groups, with increased anxiety and depressive symptoms being the most common. Two serious adverse events that were assessed as being unrelated to treatment were reported.

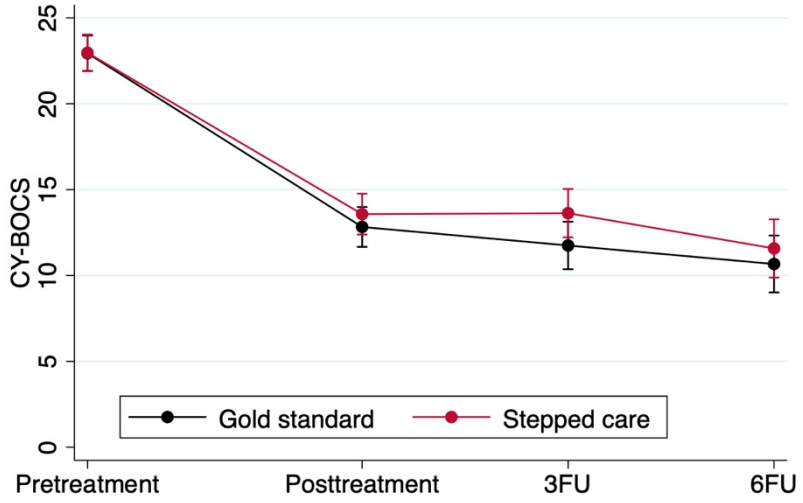

Figure 3. Effect of treatment over time on the primary outcome measure Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) with 95% confidence intervals. Scores are shown at pretreatment, posttreatment, 3-month follow-up (3FU) and 6-month follow-up (6FU).

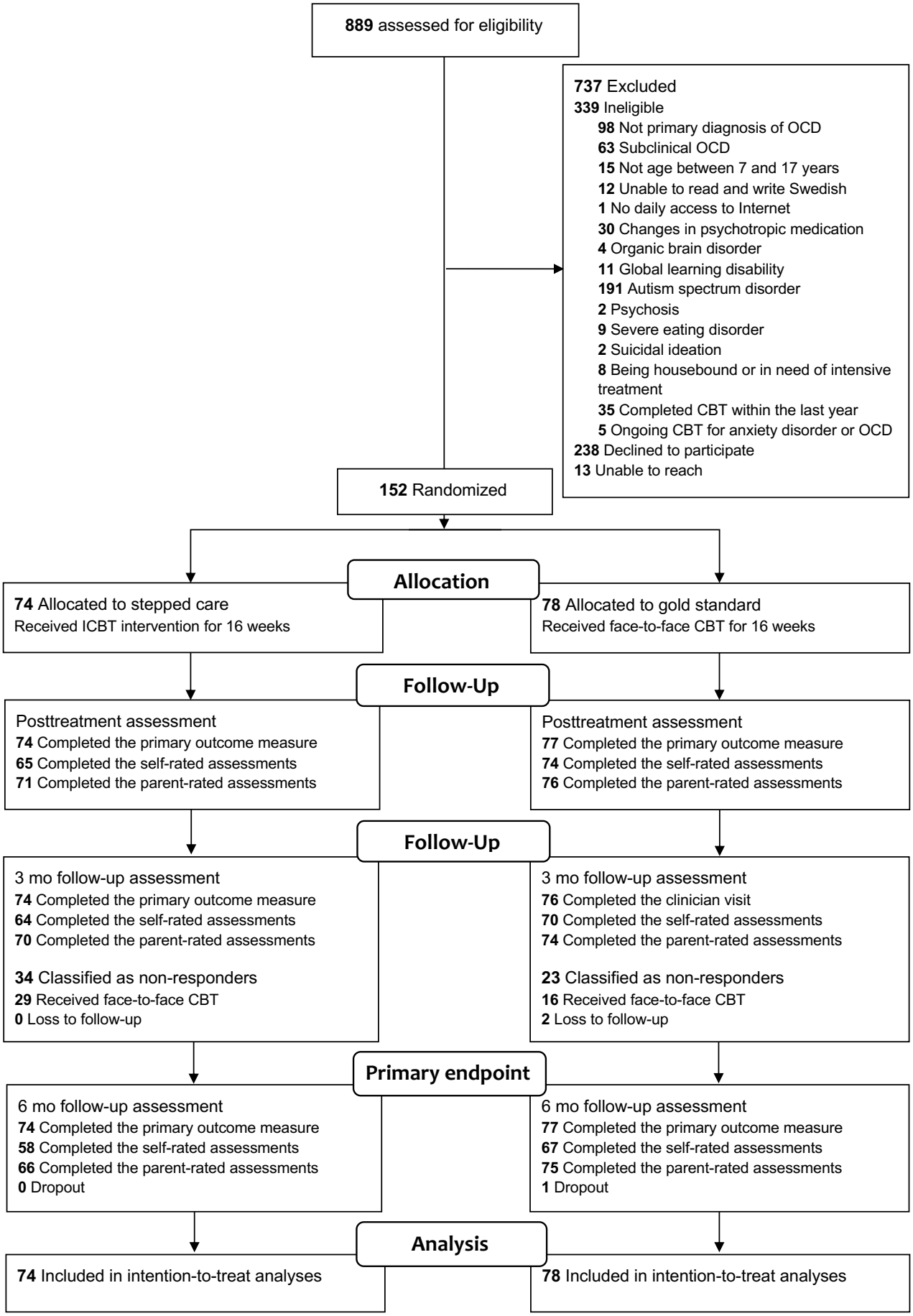

Figure 2. CONSORT flow chart for Study III.

4.5 ETHICAL CONSIDERATIONS

Ethical aspects are of high importance in research in general, and when including underaged children and adolescents in particular. All studies included in this thesis have ethical permission. Actions to ensure high ethical standard during the studies have been made, and the most central ones are regarding 1) rationale for study design, 2) recruitment including informed consent, 3) patient safety during the trials, and 4) technological aspects. The ethical considerations of these aspects are described more below.

First, there have been specific reasons behind the chosen study design in Study I-III. Prior to this project, ICBT for OCD had only been evaluated for adolescents. Therefore, it was important to conduct a smaller pilot study (Study I) for children before conducting a larger RCT, to assess the feasibility and acceptability, and to ensure that the treatment was not associated with any harmful side effects. The aim with the treatment development has been to implement it within regular CAMHS clinics. Since the treatment had so far only been evaluated within a research setting, Study II was conducted in regular clinics to ensure that the treatment also is feasible and effective when delivered in clinical units, which is important before implementation. In Study III we wanted to make a final strong test of ICBT before large-scale implementation. We chose face-to-face CBT as our control condition since there is solid evidence that this is the most effective treatment option for children and adolescents with OCD. It would be less ethical to compare ICBT with a waitlist or supportive therapy since the trial was conducted at specialist CAMHS clinics for OCD with clinician-referred patients. Based on the results from the prior trials and recommendations in guidelines, ICBT was thought to best be implemented within a stepped care model. Hence, we felt it was important to not only to evaluate ICBT compared with face-to-face CBT, but also to evaluate the whole stepped care treatment model. Ethical advantages of this was both that everyone received an active treatment including ERP, and that non-responders received additional face-to-face CBT as part of the trial.

In Study I-III, actions were taken to ensure the safety of the recruitment procedure. The participants underwent an in-depth face-to-face assessment prior to inclusion, including a diagnostic interview, medical history and interview with the CY-BOCS, to ensure that the participants had a primary diagnosis of OCD and had no more urgent mental health care condition in need of treatment (e.g., depression, eating disorder, or self-harm behavior). Prior to inclusion, families received both written and verbal information about the trial. In addition to the consent form, the participants received written information adapted to the age group specifically directed to them. They also got verbal information during the assessment to ensure that they fully understood what participation in the trial involved, and the clinicians informed them about their right to say no to participation even if the parents were interested. All participants and their caregivers provided written informed consent prior to inclusion. Patients who declined participation were offered regular treatment at the clinics according to regular clinical practice.

During Study III, we had weekly meetings with the clinicians who were involved in the trial to discuss the progress of the patients and also unexpected ethical issues to ensure the patient safety. One strength of including therapist-contact in the ICBT treatment is that the therapists have regular contact with the families and can detect worsening of symptoms. In addition, we monitored adverse events and symptom level throughout the trial. In case of deterioration, an in-depth clinician assessment was conducted and discussed within the team. In addition to offer non-responders additional face-to-face CBT as a part of the trial, we had the possibility to offer additional help at the clinic or refer participants to other appropriate service if needed. In Study III, 16% received additional treatment with CBT and/or made changes in medication during the trial period as a necessary action for the patient's wellbeing. One additional patient safety aspect of Study III was that the trial was monitored by the external party Karolinska Trial Alliance, that ensured that the recruitment of participants was conducted in an ethically sound way, and monitored safety aspects until the primary endpoint. Further, all statistical analyses were predefined in the published study protocol to enhance transparency and reduce publication bias (Appendix).

Lastly, there are several ethical considerations when it comes to technical interventions to ensure the patient integrity. Both the treatment platform where BIP OCD is delivered and the connecting platform for online self- and parent-reported measures use a double authentication procedure for both the participants and the therapists. The participants log in with a personal username and password, and receive a unique code through text message to their phone. All information in the platform is stored encrypted at a server. The clinical information about the patient and the treatment was written in their medical journal, and all sensitive material like case report forms were stored in safe cabinets at the clinics.

5 DISCUSSION

The overall aim of this thesis was to develop and evaluate novel approaches to deliver and scale up the treatment for children and adolescents with OCD.

5.1 IS ICBT A FEASIBLE INTERVENTION FOR CHILDREN WITH OCD?

Before we planned the Study I in 2015, therapist-guided ICBT had never been evaluated for children with OCD. We wanted to make CBT more available to the young people since research had shown that several years commonly pass from onset of OCD symptoms before children receive proper treatment.[13] CBT had been shown to be feasible and effective when provided through videoconferencing in one case series and one pilot trial for children with an early onset of OCD.[57,82] Further, ICBT had shown promising results for children with anxiety disorders[83,84] and functional abdominal pain,[85] and also seemed to work for adolescents with OCD.[60,61] This made us optimistic to test whether ICBT would be a feasible treatment option also for children with OCD.

The BIP OCD junior program was an adaptation of the previously developed adolescent treatment,[61] with additional videos replacing some of the text and also a shortened education part which enabled the participants to start ERP earlier during treatment. We also increased the parental involvement from five to 12 modules, since we believed this younger age group would benefit from parents taking a stronger lead in treatment as co-therapists. This is also in line with what is recommended in the literature for childhood OCD,[43] and more similar to other ICBT trials for children.[83-85] In the parental modules, we aimed to provide relevant information and necessary skills so the parents could support and reinforce their child, instead of arguing or making negative comments that would be counterproductive for the treatment. We encouraged the parents to test various reinforcement techniques and continue this important work on a daily basis.

The results showed that the families completed the majority of the modules, and they rated the treatment to be highly credible and expressed a high satisfaction afterwards. The children experienced large improvements in OCD symptom severity, functional impairment and other symptoms after treatment. The therapist time was on average 22 minutes per patient and week, which is about a third of the average time that traditional face-to-face CBT treatments consume.[22,42,43] Taken together, we considered this treatment to be acceptable, feasible and probably effective for children with OCD. This was promising as the BIP OCD program could substantially scale up the availability of CBT for this young population.

However, as the trial was conducted at the same clinical research unit as previous studies, it was unclear if the results would be maintained in other contexts as well as how it should best be implemented. This led us to investigate the next important research topic in this thesis.

5.2 CAN ICBT FOR PEDIATRIC OCD BE IMPLEMENTED IN CLINICAL UNITS?

As the effects of the BIP OCD program only had been evaluated at a specialized clinical research unit in Stockholm where it was developed,[60,61] we wanted to see if the results were

generalizable also to other contexts and countries. The main findings from Study II suggest that BIP OCD can be transferred and implemented at outpatient units. This was reflected by the overall high module completion, large reductions of OCD symptom severity, and treatment satisfaction. However, several differences between the sites highlights some important aspects that need to be considered when implementing ICBT.

One of the main differences between the sites were the number of treatment completers. The Gothenburg site stood out with 100% completers compared to the other sites with 56% completers each, even though the average module completion did not differ between the sites. One potential reason for this difference was that the Gothenburg site used the updated version of the BIP OCD program, whereas the English version of the program was based on the original adolescent version developed by Lenhard et al.[61] In practice, this means that the participants in Gothenburg started with ERP exercises at an earlier stage during treatment, which is especially interesting as adherence to ERP early in treatment have been shown to predict accelerated treatment effects during face-to-face CBT for OCD.[86,87] More research is needed to investigate if the early introduction of ERP in BIP OCD is associated with higher treatment adherence, and if higher adherence is associated with better treatment outcome also in ICBT for OCD. Further, since it can be challenging for a young person to keep up with treatment engagement throughout a treatment that is several months, parents may be needed as the engine when the motivation run short. Maybe the higher number of parental modules that were offered in the Swedish version of BIP OCD increased parental involvement in Gothenburg and led to higher treatment adherence, but this is yet a speculation and should be evaluated in future studies.

It could be argued that the quite considerable difference in treatment outline is a limitation of Study II. However, this also adds some valuable knowledge about the importance of iterative development, and that the updated program with an earlier introduction of ERP and more hands-on parental support should be the preferred version and tested in contexts outside of Sweden. Though the therapists in Gothenburg that used the updated program also spent more time communicating with the families compared to the therapists at the other two sites. The average therapist time on that particular site was more similar to what is expected in face-to-face CBT,[22,42,43] whereas the therapist time in London and Brisbane was similar to previous ICBT trials for both children (Study I) and adolescents with OCD.[60,61] These mixed results indicated a need for a larger sample and longer follow-up time to fully evaluate the efficacy and cost-effectiveness of ICBT before making recommendations about implementation.

The therapists in Study II expressed both advantages and disadvantages of the online treatment format, which was new to the them. The main advantages that were reported was convenience for both the therapists and the families, and that the parents were involved as co-therapists. Some found it more difficult to grasp how much the patients practiced their ERP exercises, and that it was more challenging to engage the participants in treatment, when they compared it to the face-to-face format that they were used to. I believe this highlights that assessing treatment adherence in ICBT is complex, and that there is a need for valuable tools in addressing this in a valuable way for both clinicians and researchers.[88] Further, maybe proper education and

continuous supervision for the therapists could override some of the above mentioned challenges when disseminating ICBT to new settings, which also have previously been stressed as important to facilitate implementation.[89,90] This could be evaluated when implementing the treatment, for example by comparing the treatment outcomes of therapists who receive both initial and continuous training in the treatment program with the outcomes of therapists who receive no additional training.

Another important feedback from the therapists was that they perceived the treatment as less suitable for those with more complex OCD symptoms (e.g., mental compulsions and rigid rules), which are also more typically found to be challenging in face-to-face treatments.[89] This could further reflect the patients that the different clinics meet, as the clinics in Gothenburg and London were specialist units for OCD that typically see more complex cases. It also underpins the perception that ICBT might not work for everyone, and that one possible treatment delivery model would be to offer it in a stepped care model where patients with more complex OCD can be offered more intensified treatment face-to-face if ICBT has not been helpful enough.

5.3 IS ICBT IN A STEPPED CARE MODEL EFFICACIOUS?

One of the major advantages of ICBT is that it could increase access to effective treatment by making the treatment equally available for those living in more rural areas with long distances to a mental health clinic as for those living in urban areas. However, ICBT might not be suitable or enough for everyone, as indicated by the lower efficacy of ICBT found in the previous BIP OCD trial by Lenhard et al.[41] compared to what is expected in standard face-to-face CBT.[41] If BIP OCD could be implemented as the first treatment step in a stepped care model, those who do not benefit sufficiently from ICBT could receive a subsequent course of face-to-face CBT.[71] Thus, after receiving the initial treatment, a careful assessment should be done to determine if the patient has received adequate response or should step up to the next more high-intensity treatment. This way the advantages of availability and reaching long-term efficacy could be combined. Despite that this approach is recommended both by experts in the field and national guidelines,[39,71] the empirical base for this approach is limited and has never been evaluated in a large-scale trial.

There are today two open trials ($N = 11$ and $N = 14$)[72,73] and one small RCT ($N = 30$)[74] that have investigated a stepped care approach for adults with OCD. Here, patients have first received bibliotherapy with low-intensity counseling as the first treatment step, and face-to-face CBT as the second step. The open trials indicated that stepped care treatment could be a feasible approach, as there was high response rates among the treatment completers, but the results were limited by high dropout rates.[72,73] The results from the RCT supported the use of a stepped care approach, but it is important to keep in mind that this study used a small sample.[74] For children, there are to my knowledge only two studies on stepped care treatment with CBT and they have been for anxiety disorders. The first study found evidence for the efficacy of bibliotherapy with limited therapist support as the first step, followed by manualized CBT treatment and lastly individualized treatment, when compared to standard CBT.[91] The

second study found that face-to-face CBT was helpful for previous non-responders to therapist-guided ICBT in an uncontrolled follow-up trial.[92]

Based on this, we felt a large-scale RCT – where our therapist-guided BIP OCD program was delivered in a stepped care model – would fill an important research gap. We chose to offer all non-responders face-to-face CBT as a second step, as this has been proven to be beneficial even after a first course of CBT in previous trials.[52,53] The results from Study III indicated that the two treatment approaches had equal treatment effects in terms of improvements of OCD symptom severity as well as on all secondary outcomes, including increased functioning and reduced family accommodating behaviors. Further, the treatment effect on OCD symptom severity did not seem to be moderated by referral source, which is promising since there have been concerns about the generalizability to clinician-referred participants in previous trials of ICBT.[60,61,93] Since the majority of participants were recruited from referrals to the two specialist OCD units, Study III further strengthen that the results of ICBT can be generalizable also to clinician-referred participants. The treatment can thus be implemented in clinical units, and should preferably be done within a stepped care model.

5.4 IS STEPPED CARE A COST-EFFECTIVE TREATMENT APPROACH?

A central aspect when it comes to implementation beside the efficacy is if the treatment is cost-effective, as this may guide health care providers and policy makers in how to allocate resources in an efficient way. ICBT for OCD has in two previous studies been found to be cost-effective for adults and adolescents with OCD,[78,79] however neither of these studies have compared ICBT with traditional treatment options. One study showed that a stepped care approach, with bibliotherapy as the first step, reduced the costs compared to providing face-to-face CBT to everyone for adults with OCD.[74] Similar findings have been shown for children with anxiety disorders.[94] We included a full health economic evaluation in Study III to evaluate the cost-effectiveness of therapist-guided ICBT in a stepped care model compared with face-to-face CBT, as this has never been done in a large-scale study before.

The results from Study III clearly indicate that the stepped care approach is cost-effective compared to traditional face-to-face CBT, as participants randomized to stepped care treatment had comparable results as in the face-to-face treatment but to a significant lower cost. Prior to the trial, we hypothesized that there would be a difference in intervention costs for the health care provider (Appendix). We could confirm this hypothesis, as the stepped care approach was associated with an average cost saving of -$2104 per patient for the total treatment period. These cost-savings were maintained even when broadening to a health care organization perspective (including other health care costs such as health care visits and medications), as well as to a societal perspective (including indirect costs such as support and assistance, school absenteeism, and parental work loss). The difference in costs were driven by the lower intervention costs in all the three perspectives.

As this is the first economic evaluation for on ICBT for OCD treatment in a stepped care model, it has important implications for the field. According to cost-effectiveness decision rules, if a

new treatment shows equal effect as a gold standard treatment but to a lower cost, the new method should be implemented, so that more costly health interventions can be reserved for patients in need of more intensive care.[95] Thus, results from Study III supports the use of therapist-guided ICBT in a stepped care model within regular health care for pediatric OCD and this approach can now be rolled out.

5.5 FUTURE DIRECTIONS

The discussed findings in this thesis provide valuable knowledge to some of the existing research gaps. In addition, the studies generated new research questions which are presented below as ideas for future research.

First, there are still a significant number of participants who do not benefit sufficiently from CBT, as 32% of the participants in Study III still had not responded after two courses of treatment and thus could be in need of additional help. This highlights the importance of continued research on treatment augmentation strategies. A next step in this field of research could be to try a sequential course of SRIs, which has received some support for non-responders after two courses of CBT in the Nordic Long-Term OCD Treatment Study (NordLOTS),[96] or to step up to an even more high-intensity treatment during four days as a third step which has been done in Norway.[97] Another possible augmentation strategy could be to detect non-responders earlier than we did in Study III and thus step up the treatment already during the first course of treatment. One way could be to identify key factors that early detect patients at risk of not responding, and randomize them to either continuing the ICBT treatment according to the existing protocol, or to receive an adapted treatment where the therapist support is intensified already during step one. This has previously been found to be helpful for adults with insomnia,[98] but is unexplored within the OCD field. Further, although Study III uses a rather long controlled follow-up time, it is still unclear how the effects of stepped care treatment stands long-term. ICBT has previously been shown to have a positive long-term effect for adolescents with OCD up to one-year posttreatment,[70] and the upcoming one-, two-, and five-year follow-up assessments in our current RCT will provide further answers to this question.

Another area that would be interesting to investigate further is the importance of parental involvement. As family accommodating behaviors are common in pediatric OCD and can affect treatment outcome negatively,[99] most CBT treatment protocols include parents to a varying extent. Further, there are studies on specific family-based CBT treatments for OCD that have positive treatment effects.[21,47] In Study I and III, family accommodation behaviors were reduced following treatment. In Study II, increased parental involvement was associated with better compliance and the therapists expressed satisfaction with having parents as co-therapists during the treatment. Future studies could thus investigate if change in parents' behaviors mediates subsequent reductions in the child's OCD symptoms, or randomize families to different degrees of parental support to investigate the role of parental involvement in more detail. Another idea for future research could be to do qualitative interviews with parents to better understand what kind of behaviors they are engaging in to help their child during treatment. This has been studied in a related research field, namely CBT for pediatric anxiety

disorders. Even though there are no overall support for the enhanced effect of involving parents in treatment of anxiety disorders,[100] parental involvement has been found to moderate treatment outcome when the focus is on contingency management and when treatment control is gradually transferred from the therapist to the parent.[101] Perhaps parental involvement is not a matter on *how much* they are involved, but rather specifically *how* they are involved. This high-resolution investigation could point out how the parental intervention could be even further improved in ICBT treatments.

A third area for future research could be to blend ICBT and face-to-face CBT. The therapists in Study II expressed a wish to add some face-to-face elements to the ICBT treatment in some cases. In Study I-III, the therapists have had the possibility to call the families and this synchronous contact was generally an appreciated feature of the treatment outline. One further development of ICBT could therefore be to provide the education part online, and then explore if providing the active treatment component ERP through either scheduled face-to-face sessions or video calls have any additional treatment effect. This is currently being pilot tested at the specialist OCD unit in Stockholm as a part of regular care, and if feasible, it could be further evaluated in a superiority trial where the blended treatment is being compared with only ICBT.

Lastly, there are still unanswered questions regarding generalizability of the results, both to other contexts, as well as to the broader spectrum of OCD patients. Currently the results of the ICBT stepped care approach is limited to Sweden, and this should be further investigated in other countries and contexts. Another issue is that both Study I-III and previous ICBT trials[60,61] have excluded patients with ASD. As seen in the flowchart of Study III (Figure 2), as much as 21% of the potential participants were excluded due to ASD. This is a limitation when it comes to generalizability, as about 17% of patients with ASD also have comorbid OCD.[102] Autism-adapted CBT[103] and function-based CBT[104] have been evaluated in a face-to-face format for patients with both ASD and OCD, but more research is needed in this area. A feasibility study is currently being conducted at our clinic where an ASD-adapted version of BIP OCD is being evaluated, with the aim of further increase availability to effective treatment for children and adolescents with OCD.

6 CONCLUSIONS

Therapist-guided ICBT is a feasible and efficacious treatment for children and adolescents with OCD, with families and therapists generally being satisfied with the treatment format. It appears that the treatment can be successfully transferrable to outpatients' clinics, but implementation should include adequate training and supervision. ICBT delivered within a stepped care model resulted in effects comparable to a full dose of face-to-face CBT, but to a lower cost for the health care provider. This should guide policy makers and health care providers on how to allocate resources. Further research should focus on evaluating treatment augmentation strategies to CBT, how to optimize the parental involvement in ICBT treatment, as well as generalizability to patients with ASD. Overall, this thesis supports a novel treatment approach for children and adolescents with OCD. ICBT is ready to be implemented as the first treatment step in a stepped care model, and can markedly increase access to CBT for children and adolescents with OCD that are in need of help.

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